

# Epidemiological studies on brassica vegetables and cancer risk.

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## Review

# Epidemiological Studies on Brassica Vegetables and Cancer Risk

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### Abstract

This paper gives an overview of the epidemiological data concerning the cancer-preventive effect of brassica vegetables, including cabbage, kale, broccoli, Brussels sprouts, and cauliflower. The protective effect of brassicas against cancer may be due to their relatively high content of glucosinolates. Certain hydrolysis products of glucosinolates have shown anticarcinogenic properties. The results of 7 cohort studies and 87 case-control studies on the association between brassica consumption and cancer risk are summarized. The cohort studies showed inverse associations between the consumption of cabbage, cauliflower, and broccoli and risk of lung cancer; between the consumption of brassicas and risk of stomach cancer; between broccoli consumption and risk of all cancers taken together; and between brassica consumption and the occurrence of second primary cancers. Of the case-control studies, 67% showed an inverse association between consumption of total brassica vegetables and risk of cancer at various sites. For cabbage, broccoli, cauliflower, and Brussels sprouts, these percentages were 70, 56, 67, and 29%, respectively. Although the measured effects might have been distorted by various types of bias, it is concluded that a high consumption of brassica vegetables is associated with a decreased risk of cancer. This association appears to be most consistent for lung, stomach, colon, and rectal cancer and least consistent for prostatic, endometrial, and ovarian cancer. It is not yet possible to resolve whether associations are to be attributed to brassica vegetables *per se* or to vegetables in general. Further epidemiological research should separate the anticarcinogenic effect of brassica vegetables from the effect of vegetables in general.

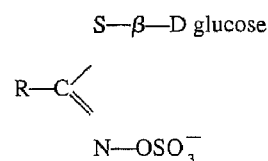
### Introduction

The consumption of vegetables and fruits has always been seen as health-promoting. In earlier times, certain vegetables and fruits were used as medicine, and now vegetables and fruits are

thought to play a protective role in the etiology of various diseases, such as cancer and coronary heart diseases. The protective effect against cancer of the consumption of a wide variety of vegetables and fruits has been examined in many epidemiological studies and has been reviewed by Block *et al.* (1) and Steinmetz and Potter (2), who concluded that there is a consistent inverse association between the consumption of a wide variety of vegetables and fruits and the risk of cancer at most sites. Raw forms seem to be the most consistently associated with lower risk.

One group of vegetables that was already used for medicinal purposes in ancient times and is now seen as possibly cancer-protective are vegetables of the family *Cruciferae* (3). The protective effect of cruciferous vegetables against cancer has been suggested to be partly due to their relatively high content of glucosinolates, which distinguishes them from other vegetables. Vegetables of the *Brassica* genus, including cabbage, kale, broccoli, cauliflower, Brussels sprouts, kohlrabi, rape, black and brown mustard, and root crops such as turnips and rutabagas (swedes) contribute most to our intake of glucosinolates (3).

Certain hydrolysis products of glucosinolates, namely indoles and isothiocyanates, have shown anticarcinogenic properties (4-6). The enzyme myrosinase, found in plant cells in a compartment separated from glucosinolates, catalyses the hydrolysis of glucosinolates (3). When the plant cells are damaged (e.g., by cutting or chewing) the myrosinase comes in contact with the glucosinolates, and hydrolysis occurs. All glucosinolates share a common basic skeleton, but differ in their side chain (R):



where R = alkyl, alkenyl, alkylthioalkyl, aryl,  $\beta$ -hydroxyalkyl, or indolylmethyl. The glucosinolate hydrolysis products consist of equimolar amounts of an aglucon, glucose, and sulfate. The aglucones are unstable and undergo further reactions to form, for instance, thiocyanates, nitriles, isothiocyanates, or indoles. In addition to depending on the conditions of the hydrolysis and the presence of any cofactors, the nature of the hydrolysis products depends primarily on the side chain of the glucosinolate. Many experimental studies have shown that indoles and isothiocyanates given to animals after a carcinogen insult reduced tumor incidence and multiplicity (see, e.g., Refs. 7-10). A possible inhibitory activity of isothiocyanates and indoles against tumorigenesis appears to stem mainly from their ability to influence phase 1 and 2 biotransformation enzyme activities, thereby influencing several processes related to chemical carcinogenesis, such as the metabolism and DNA binding of carcinogens (4-6).

The epidemiological evidence also suggests that the consumption of brassica vegetables may be inversely asso-

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Table 1 Prospective cohort studies on the consumption of brassica vegetables and cancer risk

First author and reference	Study population	Follow-up	Cancer	Exposure	RR, brassicas <sup>a</sup>	RR, total vegetables <sup>a</sup>	Confounders for which the RRs are adjusted
Kvåle, 1983 (11)	13,785 men and 2,928 women in Norway	11.5 years (113 incident cases)	Lung	Cabbage Cauliflower Rutabaga	0.6 ( $P > 0.1$ ) <sup>b,c</sup> 0.5 ( $P > 0.1$ ) <sup>b,c</sup> 1.2 ( $P > 0.1$ ) <sup>b,c</sup>	0.5 ( $P > 0.1$ ) <sup>b,c</sup>	Age, cigarette smoking, region, urban/rural place of residence
Colditz, 1985 (12)	1,271 elderly people in Massachusetts	5 years (42 deaths)	All	Broccoli	0.8 (0.4–1.6)		Age
Chyou, 1990 (13)	8,006 men of Japanese ancestry in Hawaii	18 years (111 incident cases)	Stomach	Brassica vegetables <sup>d</sup>	0.7 (0.4–1.2)	0.7 (0.4–1.1)	Age, current smoking status
Hsing, 1990 (14)	17,633 male policy holders of Lutheran Brotherhood Insurance Society (United States)	20 years (149 deaths)	Prostate	Brassica vegetables <sup>e</sup>	1.3 (0.8–2.0)	0.7 (0.4–1.2)	Age, tobacco use
Steinmetz, 1993 (15)	41,837 postmenopausal women in Iowa	4 years (138 incident cases)	Lung	Broccoli	0.7 (0.4–1.3)	0.5 (0.3–0.9)	Age, energy intake, pack-years of smoking
Steinmetz, 1994 (16)	41,837 postmenopausal women in Iowa	5 years (212 incident cases)	Colon	Brassica vegetables <sup>d</sup> Broccoli Cabbage Cauliflower Brussels sprouts	1.1 (0.7–1.7) 1.0 (0.7–1.7) 1.0 (0.5–1.7) 1.4 (0.8–2.3) 1.0 (0.7–1.6)	0.7 (0.5–1.1)	Age, energy intake
Day, 1994 (17)	1,090 oral and pharyngeal cancer patients (United States)	5 years (80 cases with second primary cancer)	Upper aerodigestive tract (39%), lung (32%), and elsewhere (29%)	Brassica vegetables <sup>f</sup>	0.6 ( $P = 0.1$ ) <sup>g</sup>	0.4 ( $P = 0.1$ ) <sup>g</sup>	Age, index tumor stage, smoking, drinking, energy intake

<sup>a</sup> RR for high versus low consumption. In parentheses, 95% CI.<sup>b</sup> RR for squamous and small-cell carcinomas.<sup>c</sup> In parentheses,  $P$  value for trend.<sup>d</sup> No specification of brassica vegetables.<sup>e</sup> Cabbage, cauliflower, and rutabaga.<sup>f</sup> Cabbage, broccoli, Brussels sprouts, and coleslaw.

ciated with risk of cancer (2). However, the evidence relating to brassicas and their bioactive compounds has not specifically been reviewed yet. In this paper, the available epidemiological data concerning the association between the consumption of brassicas and the risk of cancer will be reviewed.

## Materials and Methods

Literature searches for epidemiological studies on the relationship between the consumption of brassica vegetables and risk of cancer were performed in the following way. All epidemiological studies on the relationship between fruit and vegetable consumption and cancer risk reviewed by Steinmetz and Potter (2) and by Block *et al.* (1) were thoroughly checked to find out whether an association between brassica vegetables and cancer was specifically reported; 44 studies did report such an association. Other epidemiological studies on fruits, vegetables, and cancer were found using Medline on CD-ROM (1983–1995) and were checked in the same way, resulting in another 50 studies. The keywords, used in various combinations, were case-control, cohort, vegetable\*,<sup>2</sup> food\*, diet\*, brassica\*, crucifer\*, broccoli, cauliflower, Brussels sprouts, cabbage, cancer, and risk. Many epidemiological studies describe the vegetables

as cruciferous, when in fact they are really talking about brassica vegetables. Therefore, although in the original papers the term cruciferous is used, we now refer to the vegetables as brassicas.

In this paper, the results from prospective cohort studies are presented first, followed by the results of case-control studies, both grouped by cancer site and by type of brassica vegetable.

## Results

**Prospective Cohort Studies.** In Table 1, seven prospective cohort studies of brassica consumption and cancer risk are summarized. One cohort study reported on all cancer end points (12), and one on the occurrence of second primary cancers in oral and pharyngeal cancer patients (17). Two cohort studies reported on lung cancer (11, 15) and one each on stomach (13), prostatic (14), and colon (16) cancer. Of the seven cohort studies, five reported an inverse association between the consumption of one or more brassicas and cancer risk (11–13, 15, 17). In total, 13 associations were reported in Table 1, of which six were inverse (RRs<sup>3</sup> ranging from 0.5 to 0.8) and four were positive (RRs ranging from 1.1 to 1.4). The inverse associations were found between the

<sup>2</sup> \*\*\* denotes that the search also included compositions involving the keyword, *i.e.*, diet, dietary, diets, dietician, etc.

<sup>3</sup> The abbreviations used are: RR, relative risk; OR, odds ratio; CI, confidence interval; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.

Table 2 Case-control studies on the consumption of brassica vegetables and the risk of cancer of the respiratory tract

First author and reference	Study population	No. of cases	Exposure	Comparison	OR, brassicas <sup>a</sup>	OR, total vegetables <sup>a</sup>	Confounders for which ORs are adjusted
<b>Lung</b>							
MacLennan, 1977 (18)	♂ + ♀, Singapore	233	Mustard greens	Weekly compared to <weekly	0.6, NS		
			Kale	Weekly compared to <weekly	0.7, $P_{\text{trend}} < 0.05$		
Bond, 1987 (19) <sup>b</sup>	♂, Texas	308	Broccoli	4–6 times/week compared to never	0.3 (0.0–3.3)		Pack-years of cigarette smoking, educational level, use of vitamin supplements
Koo, 1988 (20)	♀, Hong Kong	88	Brassica vegetables <sup>c</sup>	Highest compared to lowest tertile	0.8, $P_{\text{trend}} = 0.77^d$		Age, number of live births, schooling
Fontham, 1988 (21)	♂ + ♀, Louisiana	1253	Broccoli	Highest compared to lowest tertile	0.6 (0.5–0.8)	0.8 (0.6–1.0)	Age, race, sex, pack years of cigarette smoking, family income, ethnic group, respondent status
Le Marchand, 1989 (22)	♂ + ♀, Hawaii	332	Brassica vegetables <sup>c</sup>	Highest compared to lowest quartile	♂, 0.5; $P_{\text{trend}} = 0.001$		Age, ethnicity, smoking status, pack years of cigarette smoking, cholesterol intake (for men only)
					♀, 0.2; $P_{\text{trend}} < 0.001$	♀, 0.1; $P_{\text{trend}} < 0.001$	
Mettlin, 1989 (23)	♂ + ♀, New York	569	Broccoli	>1 time/week compared to never	0.3 (0.2–0.6)		Sex, smoking history, education level
Goodman, 1992 (24)	♂ + ♀, Oahu, Hawaii	675	Broccoli	Highest compared to lowest quartile	♂, 1.0; $P_{\text{trend}} = 0.37$	♂, 0.8; $P_{\text{trend}} = 0.04$	Age at diagnosis, stage, histology, BMI <sup>f</sup> study
			Brassica vegetables <sup>c</sup>		♀, 0.5; $P_{\text{trend}} < 0.01$ ♂, 1.3; $P_{\text{trend}} = 0.93$ ♀, 1.0; $P_{\text{trend}} = 0.09$	♀, 0.5; $P_{\text{trend}} = 0.03$	
Gao, 1993 (25)	♂, Tokai area, Japan	282	Cabbage	≥3 times/week compared to almost none	0.4 (0.2–0.9)		Smoking status
Sankaranarayanan, 1994 (26)	♂, Kerala, Southern India	281	Cabbage	Daily compared to never/occasional	0.3 (0.1–1.1)		Age, education, religion, smoking
			Cauliflower	>2 times/week compared to never/occasional	1.3 (0.3–4.4)		
<b>Larynx</b>							
Graham, 1981 (27)	White ♂, New York	374	Cabbage	Information not available	No assoc.		
			Broccoli	Information not available	No assoc.		
			Brussels sprouts	Information not available	No assoc.		
Zheng, 1992 (28)	♂ + ♀, Shanghai, China	201	Brassica vegetables <sup>g</sup>	♂, highest compared to lowest tertile ♀, above compared to below median	♂, 0.7; $P_{\text{trend}} = 0.21$ ♀, 3.0 (1.0–9.2)	♂, 1.2; $P_{\text{trend}} = 0.61$ ♀, 1.1 (0.4–3.2)	Age, education, smoking

<sup>a</sup> In parentheses, 95% CI  $P_{\text{trend}}$ ,  $P$  value for  $\chi^2$  test for trend; NS, not statistically significant; ♂, males; ♀, females; no assoc., no association.

<sup>b</sup> Nested case-control study; dietary data were collected retrospectively.

<sup>c</sup> No specification of brassica vegetables.

<sup>d</sup> OR for adenocarcinomas and large-cell carcinomas; ORs for squamous carcinomas and small-cell carcinomas were less remarkable.

<sup>e</sup> Cabbage (Chinese, mustard, and head), broccoli, and bok choy.

<sup>f</sup> BMI, body mass index (kg/m<sup>2</sup>).

<sup>g</sup> Cabbage and cauliflower.

Table 3 Case-control studies on the consumption of brassica vegetables and the risk of cancer of the digestive tract

First author and reference	Study population	No. of cases	Exposure	Comparison	OR, brassicas <sup>a</sup>	OR, total vegetables <sup>a</sup>	Confounders for which ORs are adjusted
<b>Oral cavity</b>							
Marshall, 1982 (29)	White ♂, New York	427	Brassica vegetables <sup>b</sup>	Information not available	No assoc.		
Zheng, 1992 (30)	♂ + ♀, Shanghai, China	204	Brassica vegetables <sup>c</sup>	Highest compared to lowest tertile	♂, 0.8		Smoking, education
Zheng, 1993 (31)	♂ + ♀, Beijing, China	404	Cabbage	≥4/week compared to <2/month	♀, 1.5 0.8 (0.4–1.6)		Tobacco smoking, alcohol drinking, inadequate dentition, years of education, BMI, <sup>d</sup> sex, age
			Chinese cabbage	≥6/week compared to <4/month	1.5 (0.6–3.3)		
			Cauliflower	≥2/week compared to <1/month	0.2 (0.1–0.5)		
<b>Oral cavity and pharynx</b>							
McLaughlin, 1988 (32)	White ♂ + ♀, United States	871	Brassica vegetables <sup>b</sup>	Highest compared to lowest quartile	♂, 0.6; $P_{\text{trend}} = 0.006$ ♀, 0.8; $P_{\text{trend}} = 0.83$	♂, 1.0; $P_{\text{trend}} = 0.69$ ♀, 0.8; $P_{\text{trend}} = 0.20$	Smoking, alcohol drinking pattern
Gridley, 1990 (33)	Black ♂ + ♀, United States	190	Brassica vegetables <sup>c</sup>	Highest compared to lowest quartile	♂, 0.5; $P_{\text{trend}} = 0.10$ ♀, 0.2; $P_{\text{trend}} = 0.03$	♂, 0.3; $P_{\text{trend}} = 0.004$ ♀, 0.8; $P_{\text{trend}} = 0.92$	Smoking and drinking patterns, energy intake
<b>Esophagus</b>							
Wang, 1992 (34)	♂ + ♀, two areas of Shanxi, China	326	Cabbage	>3 times/week compared to <2 times per week	Yangcheng, 0.4 (0.2–0.9); Linfen, 0.9 (0.2–3.8)		Age, sex, farm/nonfarm occupation
Gao, 1994 (35)	♂ + ♀, Shanghai, China	902	Brassica vegetables <sup>b</sup>	Highest compared to lowest quartile	♂, 0.8; $P_{\text{trend}} = 0.51$ ♀, 1.1; $P_{\text{trend}} = 0.28$	♂, 0.8; $P_{\text{trend}} < 0.05$ ♀, 0.9; $P_{\text{trend}} = 0.25$	Age, education, place of birth, tea drinking, cigarette smoking, alcohol drinking
Hu, 1994 (36)	♂ + ♀, Heilongjiang Province, China	196	Chinese cabbage	Highest compared to lowest quartile	0.8 (0.4–1.7)	0.6 (0.3–1.1)	Alcohol use, smoking, income, occupation
Morris Brown, 1995 (37)	White ♂ + ♀, United States	174	Brassica vegetables <sup>f</sup>	Highest compared to lowest quartile	0.3 ( $P_{\text{trend}} < 0.001$ )	0.6 ( $P_{\text{trend}} = 0.20$ )	Age, area, smoking, liquor use, income, calories from food, BMI
<b>Stomach</b>							
Graham, 1972 (38)	White ♂ + ♀, New York	228	Coleslaw	Average monthly consumption	♂, inv. assoc. ( $P < 0.01$ ) ♀, inv. assoc. ( $P < 0.10$ )		
			Broccoli	Average monthly consumption	♂, inv. assoc. ( $P < 0.10$ )		
			Sauerkraut	Average monthly consumption	♀, inv. assoc. ( $P < 0.10$ )		
			Turnips	Average monthly consumption	♀, inv. assoc. ( $P = 0.34$ )		
			Brussels sprouts	Average monthly consumption	♀, pos. assoc. ( $P < 0.20$ )		
			Kale	Average monthly consumption	No assoc.		
			Cauliflower	Average monthly consumption	No assoc.		
			Red cabbage	Average monthly consumption	No assoc.		
Modan, 1974 (39)	♂ + ♀, Israel	166	Cabbage	Information not available	No assoc.		

Table 3 (Continued)

First author and reference	Study population	No. of cases	Exposure	Comparison	OR, brassicas <sup>a</sup>	OR, total vegetables <sup>a</sup>	Confounders for which ORs are adjusted
Correa, 1985 (40)	♂ + ♀, Louisiana	391	Broccoli	Information not available	Whites, 1.0 (0.7–1.7)	Blacks, 0.5 (0.3–1.0)	Age, sex, race, respondent status, education, income, tobacco and alcohol use
Risch, 1985 (41)	♂ + ♀, Canada	246	Brassica vegetables <sup>b</sup>	100 compared to 0 g/day	Blacks, 0.5 (0.3–0.9) 0.7 (0.4–1.1)	0.8 (0.7–1.0)	Total food consumption, ethnicity
Tajima, 1985 (42)	♂ + ♀, Japan	93	Cabbage	≥4 compared to 1 time/week	2.2 ( <i>P</i> < 0.01)		Age, sex
La Vecchia, 1987 (43)	♂ + ♀, Italy	206	Brassica vegetables <sup>b</sup>	Highest compared to lowest tertile	1.2 NS		Age, sex
Hu, 1988 (44)	♂ + ♀, China	241	Chinese cabbage	≥42 versus <42 kg/yr	0.6 (0.4–0.8)		Alcohol drinking, smoking index
Boeing, 1991 (45)	♂ + ♀, Poland	741	Cabbage	Highest compared to lowest tertile	0.6; <i>P</i> <sub>trend</sub> < 0.01	0.6; <i>P</i> <sub>trend</sub> < 0.01	Age, sex, occupation, education, residence
González, 1991 (46)	♂ + ♀, Spain	354	Cauliflower Brassica vegetables <sup>c</sup>	Highest compared to lowest tertile Highest compared to lowest quartile	0.8; <i>P</i> <sub>trend</sub> = 0.07 0.9 (0.6–1.4)	0.5; <i>P</i> <sub>trend</sub> = 0.02	Total energy, individual food items within the respective group
Hansson, 1993 (47)	♂ + ♀, Sweden	338	Rutabaga	>3 compared to <1 times/month	0.8 (0.5–1.1)	0.6 (0.4–0.9)	Age, sex, socioeconomic status
			Broccoli	>0 compared to 0 times/month	0.6 (0.4–1.0)		
			Cabbage	>2 compared to 0 times/month	0.6 (0.4–1.0)		
Ramón, 1993 (48)	♂ + ♀, Spain	117	Cabbage	Highest compared to lowest tertile	0.9	0.7	Age, sex
Colon Modan, 1975 (49)	♂ + ♀, Israel	198	Cabbage	Information not available	Inv. assoc.		
			Kohlrabi	Information not available	Inv. assoc.		
			Sauerkraut	Information not available	Inv. assoc.		
Graham, 1978 (50)	White ♂, New York	256	Cabbage	≥1 time/week compared to never	0.3 ( <i>P</i> = 0.0003)	0.5 ( <i>P</i> = 0.02)	
			Sauerkraut	Information not available	Inv. assoc.		
			Coleslaw	Information not available	Inv. assoc.		
			Brussels sprouts	Information not available	Inv. assoc.		
			Broccoli	Information not available	Inv. assoc.		
Miller, 1983 (51)	♂ + ♀, Canada	348	Brassica vegetables <sup>b</sup>	>32 compared to <11 g/day	♂, 0.9; <i>P</i> <sub>trend</sub> = 0.35 ♀, 0.7; <i>P</i> <sub>trend</sub> = 0.05	♂, 0.8; <i>P</i> <sub>trend</sub> = 0.19 ♀, 0.7; <i>P</i> <sub>trend</sub> = 0.06	Age, food group, saturated fat
			Broccoli	High compared to low	♂, 1.0; <i>P</i> <sub>trend</sub> = 0.48 ♀, 1.0; <i>P</i> <sub>trend</sub> = 0.43		
			Brussels sprouts	High compared to low	♂, 0.8; <i>P</i> <sub>trend</sub> = 0.18 ♀, 1.1; <i>P</i> <sub>trend</sub> = 0.36		
			Cabbage	High compared to low	♂, 0.8; <i>P</i> <sub>trend</sub> = 0.12 ♀, 0.9; <i>P</i> <sub>trend</sub> = 0.31		

Table 3 (Continued)

First author and reference	Study population	No. of cases	Exposure	Comparison	OR, brassicas <sup>a</sup>	OR, total vegetables <sup>a</sup>	Confounders for which ORs are adjusted
			Cauliflower	High compared to low	♂, 0.8; $P_{\text{trend}} = 0.23$		
			Turnips	High compared to low	♀, 0.8; $P_{\text{trend}} = 0.26$		
Pickle, 1984 (52)	♂ + ♀, Nebraska	58	Brassica vegetables <sup>c</sup>	≥1 compared to <1 servings/week	♂, 0.8; $P_{\text{trend}} = 0.14$ ♀, 0.9; $P_{\text{trend}} = 0.18$ 0.8 NS	1.8 NS	Bohemian ancestry, Moravian ancestry, sex, age ≥80 years, usual residence in town
Tajima, 1985 (42)	♂ + ♀, Japan	42	Cabbage	>4 compared to <1 time/week	2.1 NS		Age, sex
Kune, 1987 (53)	♂ + ♀, Australia	392	Brassica vegetables <sup>b</sup>	>425 compared to <105 g/week	0.5		Age, sex
Graham, 1988 (54)	♂ + ♀, New York	428	Brassica vegetables <sup>b</sup>	Information not available	No assoc.		
La Vecchia, 1988 (55)	♂ + ♀, Italy	339	Brassica vegetables <sup>b</sup>	Highest compared to lowest tertile	1.1 NS		Age, sex
Young, 1988 (56)	♂ + ♀, Wisconsin	353	Brassica vegetables <sup>b</sup>	Highest compared to lowest tertile	0.6 (0.4–0.9)		Age, sex, age × sex
			Cabbage	Highest compared to lowest quartile	0.8 (0.6–1.1)		
Lee, 1989 (57)	♂ + ♀, Singapore	132	Brassica vegetables <sup>b</sup>	Highest compared to lowest tertile	0.5 (0.3–0.8)	0.8 (0.5–1.3)	Age, sex, dialect group, occupational group
West, 1989 (58)	♂ + ♀, Utah	231	Brassica vegetables <sup>b</sup>	Highest compared to lowest quartile	♂, 0.3 (0.1–0.8) ♀, 0.9 (0.4–1.8) 0.5; $P_{\text{trend}} < 0.01$	♂, 0.6 (0.3–1.3) ♀, 0.3 (0.1–0.9)	Age, BMI, crude fiber, energy intake
Benito, 1990 (59)	♂ + ♀, Majorca	144	Brassica vegetables <sup>i</sup>	Highest compared to lowest quartile			Age, sex, weight 10 years prior to interview, number of years of education, job classification, physical activity on the job, number of meals/day, cereals, potatoes, meat, dairy products, eggs
Bidoli, 1992 (60)	♂ + ♀, northeastern Italy	123	Brassica vegetables <sup>b</sup>	Highest compared to lowest tertile	0.6; $\chi^2 \text{ trend} = 2.11$	0.7, $\chi^2 \text{ trend} = 1.02$	Age, sex, social status
Peters, 1992 (61)	♂ + ♀, Los Angeles County, California	746	Brassica vegetables <sup>b</sup>	RR per 10 servings per month	1.0 (1.0–1.0)		Fat, protein, carbohydrates, alcohol, calcium, family history, weight, physical activity, pregnancy history
Steinmetz, 1993 (62)	♂ + ♀, Adelaide, Australia	220	Brassica vegetables <sup>i</sup>	Highest compared to lowest quartile	♂, 1.2 (0.6–2.1) ♀, 0.9 (0.4–1.8)	♂, 1.2 (0.6–2.2)	Protein intake
			Broccoli	Highest compared to lowest tertile	♂, 0.9 (0.5–1.7)		
			Cabbage	Highest compared to lowest quartile	♀, 1.0 (0.5–1.9) ♂, 0.8 (0.4–1.5)		
			Cauliflower	Highest compared to lowest quartile	♀, 0.7 (0.3–1.5) ♂, 1.8 (1.0–3.3) ♀, 1.1 (0.5–2.2)		

Table 3 (Continued)

First author and reference	Study population	No. of cases	Exposure	Comparison	OR, brassicas <sup>a</sup>	OR, total vegetables <sup>a</sup>	Confounders for which ORs are adjusted
<b>Rectum</b>							
Graham, 1978 (50)	White ♂, New York	330	Cabbage	≥1 time/week compared to never	0.7 ( <i>P</i> = 0.05)	1.7 ( <i>P</i> = 0.12)	
			Sauerkraut	Information not available	No assoc.		
			Coleslaw	Information not available	No assoc.		
			Brussels sprouts	Information not available	No assoc.		
			Broccoli	Information not available	No assoc.		
Miller, 1983 (51)	♂ + ♀, Canada	194	Brassica vegetables <sup>b</sup>	>32 compared to <11 g/day	♂, 0.9; <i>P</i> <sub>trend</sub> = 0.28 ♀, 0.8; <i>P</i> <sub>trend</sub> = 0.26	♂, 1.1; <i>P</i> <sub>trend</sub> = 0.43 ♀, 1.2; <i>P</i> <sub>trend</sub> = 0.28	Age, food group, saturated fat
			Broccoli	High compared to low	♂, 1.0; <i>P</i> <sub>trend</sub> = 0.34 ♀, 1.2; <i>P</i> <sub>trend</sub> = 0.29		
			Brussels sprouts	High compared to low	♂, 1.6; <i>P</i> <sub>trend</sub> = 0.07 ♀, 1.5; <i>P</i> <sub>trend</sub> = 0.26		
			Cabbage	High compared to low	♂, 0.9; <i>P</i> <sub>trend</sub> = 0.27 ♀, 0.6; <i>P</i> <sub>trend</sub> = 0.08		
			Cauliflower	High compared to low	♂, 1.0; <i>P</i> <sub>trend</sub> = 0.38 ♀, 1.2; <i>P</i> <sub>trend</sub> = 0.25		
			Turnips	High compared to low	♂, 0.6; <i>P</i> <sub>trend</sub> = 0.04 ♀, 1.1; <i>P</i> <sub>trend</sub> = 0.24		
Pickle, 1984 (52)	♂ + ♀, Nebraska	28	Brassica vegetables <sup>c</sup>	≥1 servings/week compared to <1 servings/week	1.2 NS	1.4 NS	Bohemian ancestry, Moravian ancestry, sex, age ≥ 80 years, usual residence in town
Tajima, 1985 (42)	♂ + ♀, Japan	51	Cabbage	>4 compared to <1 time/week	1.0 NS		Age, sex
Kune, 1987 (53)	♂ + ♀, Australia	323	Brassica vegetables <sup>b</sup>	>425 compared to <105 g/week	0.6		Age, sex
La Vecchia, 1988 (55)	♂ + ♀, Italy	236	Brassica vegetables <sup>b</sup>	Highest compared to lowest tertile	0.9, NS		Age, sex
Lee, 1989 (57)	♂ + ♀, Singapore	71	Brassica vegetables <sup>b</sup>	Highest compared to lowest tertile	0.5 (0.3–1.0)	0.5 (0.3–1.0)	Age, sex, dialect group, occupational group
Benito, 1990 (59)	♂ + ♀, Majorca	130	Brassica vegetables <sup>d</sup>	Highest compared to lowest quartile	0.5; <i>P</i> <sub>trend</sub> < 0.05		Age, sex, weight 10 years prior to interview, number of years of education, job classification, physical activity on the job, number of meals/day, cereals, potatoes, meat, dairy products, eggs
Freudenheim, 1990 (63)	White ♂ + ♀, New York	422	Broccoli	Information not available	♂, inv. assoc. ♀, no assoc.		
Bidoli, 1992 (60)	♂ + ♀, northeastern Italy	125	Brassica vegetables <sup>b</sup>	Highest compared to lowest tertile	0.6; $\chi^2$ trend = 3.10	0.6; $\chi^2$ trend = 1.24	Age, sex, social status
<b>Colorectum</b>							
Zaridze, 1993 (64)	♂ + ♀, Moscow and Khabarovsk, Russia	117	Cabbage	Highest compared to lowest quartile	1.0 (0.5–2.0)	0.3 (0.1–0.6)	Energy intake, education
Freedman, 1995 (65)	♂ + ♀, New York	163	Brassica vegetables <sup>b</sup>	Highest compared to lowest quartile	0.6 (0.3–1.0)		



Table 3 (Continued)

First author and reference	Study population	No. of cases	Exposure	Comparison	OR, brassicas <sup>a</sup>	OR, total vegetables <sup>a</sup>	Confounders for which ORs are adjusted
Colorectal polyps							
Hoff, 1986 (66)	♂ + ♀, Norway	155	Brassica vegetables <sup>k</sup>	Mean daily intake (g/10 MJ)	inv. assoc.		
Kune, 1991 (67)	♂ + ♀, Melbourne, Australia	49	Brassica vegetables <sup>b</sup>	♂, >192 compared to ≤192 g/week	0.6 (0.3–1.2)		
				♀, >385 compared to ≤385 g/week			
Benito, 1993 (68)	♂ + ♀, Majorca	101	Brassica vegetables <sup>c</sup>	Highest compared to lowest quartile	0.6; $\chi^2$ trend = 2.22	0.2; $P_{\text{trend}} < 0.01$	Age, sex, physical activity, rural residence
Witte, 1995 (69)	♂ + ♀, Los Angeles	488	Brassica vegetables <sup>b</sup>	Highest compared to lowest quintile	0.5 (0.3–0.9)	0.5 (0.3–0.9)	Matching variables, race, BMI <sup>d</sup> , physical activity, smoking energy, saturated fat
			Broccoli		0.6 (0.4–0.9)		
			Cauliflower		0.8 (0.5–1.1)		
Biliary tract							
Moerman, 1995 (70)	♂ + ♀, the Netherlands	111	Brassica vegetables <sup>f</sup>	Highest compared to lowest tertile	0.6 (0.3–1.0)	0.4 (0.2–0.7)	Sex, age class, response status, BMI, smoking status
Pancreas							
Olsen, 1989 (71), 1991 (72)	White ♂, Minnesota	212	Brassica vegetables <sup>k</sup>	≥9 compared to ≤2 times/month	0.6 (0.3–1.0)		Age, education level, diabetes mellitus, cigarette smoking, alcohol, meat and/or vegetable consumption
Bueno de Mesquita, 1991 (73)	♂ + ♀, the Netherlands	164	Brassica vegetables <sup>f</sup>	Highest compared to lowest quintile	0.3; $P_{\text{trend}} < 0.05$	0.3; $P_{\text{trend}} < 0.05$	Age, gender, response status, total smoking, total energy intake
Ji, 1995 (74)	♂ + ♀, Shanghai, China	451	Brassica vegetables <sup>m</sup>	Highest compared to lowest quartile	♂, 0.8 (0.5–1.2) ♀, 1.1 (0.6–1.8)	♂, 0.7 (0.5–1.0) ♀, 0.7 (0.4–1.1)	Age, income, smoking, green tea drinking (women only), response status

<sup>a</sup> In parentheses, *P* values or 95% CI;  $P_{\text{trend}}$ , *P* value for  $\chi^2$  test for trend; NS, not statistically significant; inv. assoc., inverse association; pos. assoc., positive association; no assoc., no association; ♂, male; ♀, female.

<sup>b</sup> No specification of brassica vegetables.

<sup>c</sup> Cabbage and cauliflower.

<sup>d</sup> BMI, body mass index (kg/m<sup>2</sup>).

<sup>e</sup> Cabbage, broccoli, Brussels sprouts, and coleslaw.

<sup>f</sup> Cabbage (cooked), broccoli, cauliflower, coleslaw, collard and mustard greens, and kale.

<sup>g</sup> Cabbage, broccoli, and Brussels sprouts.

<sup>h</sup> Cabbage, broccoli, Brussels sprouts, cauliflower, and sauerkraut.

<sup>i</sup> Cabbage, Brussels sprouts, and cauliflower.

<sup>j</sup> Cabbage, broccoli, Brussels sprouts, cauliflower, coleslaw, and root vegetables.

<sup>k</sup> Cabbage, broccoli, Brussels sprouts, and cauliflower.

<sup>l</sup> Cabbage, Brussels sprouts, cauliflower, sauerkraut, and kale.

<sup>m</sup> Cabbage, Chinese cabbage, Shanghai bok choy, and cauliflower.

consumption of cabbage, cauliflower, and broccoli and risk of lung cancer (11, 15), between consumption of brassicas and risk of stomach cancer (13), between consumption of broccoli and risk of all cancers taken together (12), and between consumption of brassicas and the occurrence of second primary cancers (17). The positive associations were found between the consumption of rutabaga (swede) and lung cancer risk (11), between brassicas and cauliflower and colon cancer risk (16), and between brassicas and risk of prostatic cancer (14). Of all these associations, both positive and inverse, none was statistically significant.

**Case-Control Studies.** A total of 87 case-control studies on the association between consumption of brassica vegetables and cancer risk were identified (Tables 2–5). Of these, 68 (78%) found lower cancer risk to be associated with consumption of one or more brassicas in at least one sex, although many associations were not significant. Table 6 presents a summary of the number of case-control studies finding inverse, positive, or no associations between cancer risk and consumption of the most examined brassica vegetables, grouped by vegetable type. Of the studies examining the effect of consumption of total brassica vegetables on cancer risk, 67% showed an inverse

association (of which 51% was significant) for both men and women for various cancer sites. For cabbage, broccoli, cauliflower, and Brussels sprouts the percentages of studies with inverse associations were 70, 56, 67, and 29%, respectively. Of these inverse associations, 41, 70, 25, and 0% were significant, respectively.

Most evidence for the association between the consumption of brassica vegetables and risk of cancer is available for colon, stomach, rectal, and lung cancer. For these cancer sites, Table 7 presents a summary of the number of case-control studies finding (significant) inverse and positive associations between cancer risk and consumption of one or more brassica vegetables. Of the studies on colon cancer, 73% reported at least one inverse association, and 55% of these studies showed at least one significant inverse association. For stomach, rectal, and lung cancer, the percentages of studies showing at least one inverse association were 73, 80, and 100%, respectively. Of these studies, 63, 50, and 67% showed at least one significant inverse association, respectively. For cancer sites not mentioned in Table 7, only very few studies were conducted. All studies on cancer of the esophagus, thyroid, oral cavity and pharynx, and pancreas, as well as all studies on colorectal polyps (which are potential precursors of colorectal cancer), showed at least one inverse association with consumption of brassicas, although some associations were not significant. The least consistent results were seen in studies on cancer of the endometrium, ovary, and prostate.

## Discussion

We have attempted to give a complete overview of the epidemiological studies on the association between brassica consumption and cancer risk. No doubt, there are studies that have collected data pertaining to this association but that cannot be included in this overview because such an association was not reported. Besides, publication bias may have occurred because null findings may remain unpublished as a result of their alleged lack of scientific interest.

The following should be taken into account when interpreting the results of the studies. In case-control studies the measured effect can be distorted by selection bias, resulting from procedures used to select subjects (both cases and controls). As a result of selection bias, the relationship between exposure and disease is different for those who participate in the study and those who would be theoretically eligible but do not participate. For example, controls with a high health consciousness who eat vegetables on a regular basis may be more inclined to participate in studies on cancer than controls with a weaker health consciousness who eat fewer vegetables. Furthermore, in case-control studies, dietary information is collected retrospectively from cases. The disease process may have influenced consumption or knowledge of the disease status may have resulted in recall bias in patients, both potentially introducing differential misclassification. Exaggeration of the association between brassica consumption and cancer risk may have occurred in the case-control studies as a result of recall bias if cases, but not controls, reported a lower consumption of vegetables than they actually did consume or as a result of a lower vegetable consumption due to the disease. In prospective studies, problems of such differential misclassification are avoided because dietary intake is measured a number of years before diagnosis. Both selection bias and recall bias could have accounted for part of the inverse associations observed in many case-control studies.

The results of both case-control and cohort studies may be

influenced by a rather crude assessment of vegetable consumption, leading to nondifferential misclassification of exposure. When a true association exists between vegetable consumption and cancer risk, bias from this type of misclassification can result in underestimation of the strength of that association. In this overview, prospective studies found weaker inverse associations between brassica consumption and risk of cancer than did case-control studies. Besides, from the absence of differential bias, this weaker association might be explained by a larger role of nondifferential misclassification in prospective studies due to a more crude estimation of food intake compared to most case-control studies.

In many studies, especially the older ones, the effect of brassica vegetables was not fully adjusted for confounders associated with the cancer studied, possibly resulting in a distortion of the association between brassica consumption and cancer risk. When correction for confounders was made, residual confounding may still have been present. This is the case when the confounder is not measured adequately, leaving it still affecting the association after correction. This is a possible problem in smoking-induced cancers. In many populations, smokers tend to eat fewer vegetables and fruits than do non-smokers (95). Controlling for the confounding effect of smoking should be done adequately to find the true association between vegetable and fruit consumption and risk of cancer.

The consumption of brassica vegetables is most probably positively correlated with the total consumption of vegetables and the consumption of other vegetables. In hardly any epidemiological studies was the effect of brassica vegetables separated from the effect of total vegetables or other vegetables by adjusting for the consumption of these vegetables. Therefore, it is difficult to sort out whether the observed association was attributable to brassica vegetables, to vegetables as a whole, or to other vegetables.

Many studies mentioned in this review showed an inverse association between the consumption of various brassica vegetables and cancer risk. The results of the epidemiological studies agree with results of experimental studies in which brassica vegetables reduced mammary tumor incidence (96–99), hepatic tumor size (100), number of tumors per liver (101), tumor frequency (102), and the number of pulmonary metastases (103) when given to rodents before (96–97, 99) or after (98, 100–103) a carcinogen insult. The relatively high glucosinolate content of brassicas has been suggested to partly cause the anticarcinogenic effects, because certain hydrolysis products of glucosinolates, namely indoles and isothiocyanates, have shown anticarcinogenic properties (4–6). The possible anticarcinogenic activities of isothiocyanates and indoles appears to stem mainly from their ability to influence phase 1 and 2 biotransformation enzyme activities (4–6). Phase 1 and 2 biotransformation enzymes are involved in the modulation of metabolism of carcinogenic/mutagenic compounds, thereby preventing the formation of electrophilic intermediates (104). Electrophilic intermediates can bind to DNA. If repair of the damage does not occur, replication of DNA can lead to permanent DNA lesion and, in presence of a tumor promotor, to preneoplastic cells, neoplastic cells, and finally metastases (105). Phase 1 involves oxidation, reduction, and hydrolysis reactions, thereby making xenobiotics more hydrophilic (which can result in inhibition of activation but also in activation of the compound) as well as susceptible to detoxification. Phase 2 metabolism, a detoxifying mechanism, comprises conjugation reactions making phase 1 metabolites more polar and readily excretable (104). In *in vivo* experiments with rodents, brassica vegetables induced the phase 1 enzymes aryl hydrocarbon

Table 4 Case-control studies on the consumption of brassica vegetables and the risk of cancer of reproductive organs

First author and reference	Study population	No. of cases	Exposure	Comparison	OR, brassicas <sup>a</sup>	OR, total vegetables <sup>a</sup>	Confounders for which ORs are adjusted
<b>Cervix</b>							
Marshall, 1983 (75)	White ♀, New York	513	Brassica vegetables <sup>b</sup>	≥16 compared to 0–3 times/month	1.9 (1.2–3.0)		
<b>Endometrium</b>							
Barbone, 1993 (76)	♀, Birmingham, Alabama	168	Broccoli	≥1/month compared to <1/month	0.5 (0.3–1.0)		Age, years of schooling, total energy, use of unopposed estrogens, obesity, shape of obesity, smoking, age at menarche, age at menopause, number of pregnancies, diabetes, hypertension
			Cauliflower	≥1/month compared to <1/month	0.5 (0.3–0.8)		
Levi, 1993 (77)	♀, northern Italy and Vaud, Switzerland	274	Brassica vegetables <sup>b</sup>	Highest compared to lowest tertile of Frequency consumption	1.2; $\chi^2$ trend = 0.43	0.6; $\chi^2$ trend = 4.14	Study center, age
Shu, 1993 (78)	♀, Shanghai, China	268	Brassica vegetables <sup>c</sup>	Highest compared to lowest quartile	1.1; $P_{\text{trend}} = 0.67$	1.4; $P_{\text{trend}} = 0.39$	Age, number of pregnancies, BMI <sup>d</sup> , total calories
<b>Ovary</b>							
Byers, 1983 (79)	White ♀, New York	274	Brassica vegetables <sup>b</sup>	Highest compared to lowest tertile	0.8; $P_{\text{trend}} < 0.10$		Age
Shu, 1989 (80)	♀, Shanghai, China	172	Brassica vegetables <sup>c</sup>	Highest compared to lowest quartile	1.2; $P_{\text{trend}} = 0.55$	0.8; $P_{\text{trend}} = 0.45$	Education
<b>Breast</b>							
Graham, 1982 (81)	White ♀, New York	2024	Brassica vegetables <sup>f</sup>	≥20 compared to 0–3 times/month	1.0 NS		
Katsouyanni, 1986 (82)	♀, Greece	120	Cabbage, raw		$\chi^2$ trend = 2.60		Age, interviewer, years of schooling
			Cabbage, cooked		( $P < 0.05$ ) $\chi^2$ trend = 1.32		
			Broccoli		$\chi^2$ trend = 0.26		
			Cauliflower		$\chi^2$ trend = 1.77		
Levi, 1993 (83)	♀, Vaud, Switzerland	107	Brassica vegetables <sup>b</sup>	Highest compared to lowest tertile	0.5; $P_{\text{trend}} < 0.05$		Age, education, total energy intake
<b>Prostate</b>							
Schuman, 1982 (84)	White ♂, Minneapolis	223	Cabbage	≥6 times/month compared to never	0.7 NS		
			Cauliflower	≥3 times/month compared to never	0.8 NS		
			Rutabaga and kohlrabi	≥1 time/month compared to never	1.0 NS		
Graham, 1983 (85)	White ♂, New York	262	Brassica vegetables <sup>b</sup>	Highest compared to lowest frequency quartile	1.1; $P_{\text{trend}} > 0.05$		
Le Marchand, 1991 (86)	♂, Hawaii	452	Brassica vegetables <sup>g</sup>	Highest compared to lowest quartile	1.1; $P_{\text{trend}} = 0.40^h$	1.2; $P_{\text{trend}} = 0.58^h$	Age, ethnicity

<sup>a</sup> In parentheses,  $P$  value or 95% CI;  $P_{\text{trend}}$ ,  $P$  value for  $\chi^2$  test for trend; NS, not statistically significant; ♂, male; ♀, female.

<sup>b</sup> No specification of brassica vegetables.

<sup>c</sup> Cabbage and cauliflower.

<sup>d</sup> BMI, body mass index ( $\text{kg}/\text{m}^2$ ).

<sup>e</sup> Cabbage, cauliflower, and greens.

<sup>f</sup> Cabbage, broccoli, Brussels sprouts, coleslaw, sauerkraut, and turnips.

<sup>g</sup> Cabbage (Chinese, mustard, and head), broccoli, and bok choy.

<sup>h</sup> OR for age group ≥70; no significant associations were found for age group <70.

hydroxylase (106–109), benzo[*a*]pyrene hydroxylase (110, 111), 7-ethoxycoumarin *O*-deethylase (106–108, 110), 7-ethoxyresorufin *O*-deethylase (112–114), and 7-pentoxoresorufin *O*-dealkylase (114) and the phase 2 enzymes epoxide hydrolase (106–109, 115), glutathione *S*-transferase

(106–109, 114, 116–119), NADPH-quinone reductase (114), and UDP glucuronyl transferase (114). Brussels sprouts and cabbage also reduced binding of aflatoxin B<sub>1</sub> to DNA in *in vivo* experiments with rats (108, 118). When given to humans, Brussels sprouts reduced oxidative DNA damage (120) and

Table 5 Case-control studies on the consumption of brassica vegetables and the risk of miscellaneous cancer sites

First author and reference	Study population	No. of cases	Exposure	Comparison	OR, brassicas <sup>a</sup>	OR, total vegetables <sup>a</sup>	Confounders for which ORs are adjusted
Thyroid							
Ron, 1987 (87)	♂ + ♀, Connecticut	159	Cabbage	Few times/week or daily compared to never or few times/year	0.8; $P_{\text{trend}} = 0.14$		Age, sex, prior radiotherapy to the head and neck, thyroid nodules, and goiter
			Brussels sprouts	Few times/week or daily compared to never or few times/year	0.7; $P_{\text{trend}} = 0.13$		
			Cauliflower	Few times/week or daily compared to never or few times/year	0.8; $P_{\text{trend}} = 0.29$		
			Broccoli	Few times/week or daily compared to never or few times/year	0.8; $P_{\text{trend}} = 0.20$		
Franceschi, 1989 (88)	♂ + ♀, northern Italy	245	Brassica vegetables <sup>b</sup>	Highest compared to lowest tertile	0.7; $\chi^2 \text{ trend} = 1.96$		Age, sex, geographical area
Franceschi, 1991 (89)	♂ + ♀, northern Italy and Vaud, Switzerland	385	Brassica vegetables <sup>b</sup>	Highest compared to lowest tertile	0.8; $\chi^2 \text{ trend} = 1.59$		
Wingren, 1993 (90)	Southeastern Sweden	93	Brassica vegetables <sup>b</sup>	Several times/week compared to seldom/never	0.2 (0.1–0.8)		
Bladder							
Metlin, 1979 (91)	White ♂ + ♀, New York	569	Brassica vegetables <sup>c</sup>	≥15 compared to 0–4 times/month	0.8; $P_{\text{trend}} > 0.05$		Sex
Nasal cavity and sinuses							
Zheng, 1992 (92)	♂ + ♀, Shanghai, China	60	Brassica vegetables <sup>b</sup>	Highest compared to lowest tertile	0.9 (0.5–1.8)		Age
Mesothelium							
Schiffman, 1988 (93)	♂ + ♀, Louisiana	37	Brassica vegetables <sup>b</sup>	Highest compared to lowest tertile	0.2 (0.03–1.0)	0.3 (0.1–1.8)	Asbestos exposure
Skin, nonmelanoma							
Kune, 1992 (94)	♂, Melbourne, Australia	88	Brassica vegetables <sup>d</sup>	>1 servings/week compared to ≤1 servings/week	0.1 (0.1–0.3)		Age

<sup>a</sup> In parentheses, 95% CI;  $P_{\text{trend}}$ ,  $P$  value for  $\chi^2$  test for trend; ♂, male; ♀, female.

<sup>b</sup> No specification of brassica vegetables.

<sup>c</sup> Cabbage, broccoli, Brussels sprouts, cauliflower, coleslaw, turnips, and parsnips.

<sup>d</sup> Cabbage, broccoli, and Brussels sprouts.

elevated plasma glutathione *S*-transferase- $\alpha$  (121, 122) and rectal glutathione *S*-transferase- $\alpha$  and - $\pi$  levels (123), and broccoli induced the P450 1A2 (phase 1) activity (124–125).

The effect of brassica consumption on cancer risk may differ among different cancer sites. In this review, brassica consumption appeared to be especially associated with cancers of the digestive and respiratory tract. For hormone-dependent cancers, this association appeared to be less consistent, although only a few studies were conducted. It has been suggested that the risk of estrogen-dependent diseases such as mammary cancer may also be reduced by brassica vegetables through the intake of indoles (126). Indoles induce the phase 1 enzyme estradiol 2-hydroxylase. This leads to the biotransformation of estradiol to 2-hydroxyestrone, which has a minimal estrogenic activity (127). When indole-3-carbinol, a hydrolysis product of the glucosinolate glucobrassicin, was given to humans, an increase of the estradiol 2-hydroxylation (128, 129) and of the 2-hydroxy-estrone:estrone ratio (130) was seen.

Some epidemiological studies examined the association between brassica consumption and lung cancer risk within smoking strata, but the results were inconsistent. Gao *et al.* (25) found a significant inverse association between cabbage consumption and lung cancer risk among current smokers (OR, 0.3; 95% CI, 0.1–1.0). Among ex-smokers and nonsmokers the

inverse association was also present, but did not reach significance (ORs, 0.7 and 0.5; 95% CIs, 0.2–2.1 and 0.1–3.1, respectively). Steinmetz *et al.* (15) found an inverse association between broccoli consumption and risk of lung cancer among ex-smokers (OR, 0.4; 95% CI, 0.1–1.1), no association among current smokers (OR, 1.0; 95% CI, 0.4–2.1), and a nonsignificant positive association among nonsmokers (OR, 2.0; 95% CI, 0.4–11.2). Koo (20) examined the association between brassica consumption and lung cancer risk among women who had never smoked. No such association was found (OR, 1.0;  $P$  value for trend, 0.4). It has been suggested that exposure to tobacco-specific nitrosamines, formed from the nitrosation of nicotine during tobacco processing and cigarette smoking, is a causative factor in several cancers (131). NNK, a potent tobacco-specific carcinogen, induced lung tumors in all laboratory animal species tested (131). DNA methylation is believed to be mainly responsible for the potent carcinogenicity of NNK. To form reactive electrophilic species for binding to DNA, NNK requires metabolic activation. Although the effect of brassicas on NNK metabolism has not been examined yet, the effect of isothiocyanates has often been examined. In several *in vitro* and *in vivo* studies, isothiocyanates were shown to be potent inhibitors of NNK metabolism (132–139) and DNA methylation by NNK (7, 138, 140–142). In *in vivo* studies, isothiocyanates

Table 6 Summary of the results of case-control studies concerning the association between brassica consumption and cancer risk, by vegetable type

Type of vegetable	Total number of studies	Number of studies showing an inverse association <sup>a</sup>	Number of studies showing no association	Number of studies showing a positive association <sup>b</sup>	Studies showing a different association for women and men
Brassicas	58	39 (67%)	4 (7%)	9 (16%)	1 ♀ inv. assoc., ♂ pos. assoc. <sup>d</sup> 1 ♀ no assoc., ♂ pos. assoc. 4 ♀ pos. assoc., <sup>e</sup> ♂ inv. assoc.
Cabbage <sup>f</sup>	24	17 (70%)	5 (20%)	2 (10%)	
Broccoli	18	10 (56%)	3 (17%)	1 (6%)	1 ♀ inv. assoc., <sup>g</sup> ♂ no assoc. 2 ♀ no assoc., ♂ inv. assoc. 1 ♀ pos. assoc., ♂ no assoc.
Cauliflower	12	8 (67%)	1 (8%)	2 (17%)	1 ♀ pos. assoc., ♂ no assoc.
Brussels sprouts	7	2 (29%)	2 (29%)	2 (29%)	1 ♀ pos. assoc., ♂ inv. assoc.

<sup>a</sup> Number of studies in which the inverse association was statistically significant (expressed as significant studies/total studies); brassicas, 20/39 (2 of the 20 studies reported a statistically significant inverse association for ♀ only, 2 studies only for ♂), cabbage, 7/17; broccoli, 7/10; cauliflower, 2/8; Brussels sprouts, 0/2.

<sup>b</sup> Number of studies in which the positive association was statistically significant (expressed as significant studies/total studies); brassicas, 1/9; cabbage, 1/2; broccoli, 0/1; cauliflower, 0/2; Brussels sprouts, 0/1.

<sup>c</sup> These studies are not included in earlier columns, except in the first column showing the total number of studies.

<sup>d</sup> Inv. assoc., inverse association; pos. assoc., positive association; no assoc., no association.

<sup>e</sup> One of the positive associations was statistically significant.

<sup>f</sup> Not including Chinese cabbage.

<sup>g</sup> Statistically significant inverse association.

Table 7 Summary of results of case-control studies concerning the association between consumption of brassica vegetables and cancer risk, by cancer site

Cancer site	Total number of studies	Number of studies showing an inverse association for one or more brassicas <sup>a</sup>	Number of studies showing a positive association for one or more brassicas <sup>b</sup>
Colon	15	11 (73%)	4 (27%)
Stomach	11	8 (73%)	3 (27%)
Rectum	10	8 (80%)	3 (33%)
Lung	9	9 (100%)	2 (22%)

<sup>a</sup> Number of studies in which at least one inverse association was statistically significant (expressed as significant studies/total studies): colon, 6/11; stomach, 5/8; rectum, 4/8; lung, 6/9.

<sup>b</sup> Number of studies in which at least one positive association was statistically significant (expressed as significant studies/total studies): colon, 0/4; stomach, 1/3; rectum, 0/3; lung, 0/2.

reduced lung tumor incidence when given before NNK (7, 138, 141–145). The inhibitory action of the isothiocyanates is believed to be due to competitive inhibition and an inactivation of the P450 enzyme(s) responsible for the metabolic activation of NNK (137).

The anticarcinogenic effects of brassicas have been suggested to be partly due to their relatively high glucosinolate content. In addition to glucosinolates, brassica vegetables also contain many other compounds for which protective mechanisms have been postulated (*e.g.*, carotenoids, vitamin C, folic acid, dietary fiber, and protease inhibitors; Ref. 146). Therefore, it should be noted that the observed protective effects of brassicas may be caused by other compounds, whether in combination with glucosinolates or not.

## Conclusion

In general, there seems to be an inverse association between the consumption of brassica vegetables and the risk of cancer. Although case-control studies may carry some risk of bias, overwhelmingly inverse results suggest that at least part of the

association is real. This association appears to be most consistent for lung, stomach, colon, and rectal cancer, and least consistent for prostatic, endometrial, and ovarian cancer. The few cohort studies conducted confirm the inverse association, in particular for lung and stomach cancer.

It is not yet possible to decide whether the protective effect is attributable to brassica vegetables *per se* or to vegetables in general. Therefore, further epidemiological research should examine the effect of the consumption of brassicas on the risk of cancer, with specific attention to simultaneous modeling of different vegetables (or vegetable groups) and adjustment for confounding due to other determinants and vegetables in general. Besides, more epidemiological studies should examine the association between brassica consumption and the risk of hormone-dependent cancers, as well as the association between brassica consumption and cancer risk within smoking strata.

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